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REVIEW ARTICLE

Restoration of sensorimotor functions after spinal cord injury

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The purpose of this review is to discuss the achievements and perspectives regarding rehabilitation of sensorimotor functions after spinal cord injury. In the first part we discuss clinical approaches based on neuroplasticity, a term referring to all adaptive and maladaptive changes within the sensorimotor systems triggered by a spinal cord injury. Neuroplasticity can be facilitated through the training of movements with assistance as needed, and/or by electrical stimulation techniques. The success of such training in individuals with incomplete spinal cord injury critically depends on the presence of physiological proprioceptive input to the spinal cord leading to meaningful muscle activations during movement performances. The addition of rehabilitation technology, such as robotic devices allows for longer training times and provision of feedback information regarding changes in movement performance. Nevertheless, the improvement of function by such approaches for rehabilitation is limited. In the second part, we discuss preclinical approaches to restore function by compensating for the loss of descending input to spinal networks following complete spinal cord injury. This can be achieved with stimulation of spinal networks or approaches to restore their descending input. Electrical and pharmacological stimulation of spinal neural networks is still in an experimental stage; and despite promising repair studies in animal models, translations to humans up to now have not been convincing. It is likely that combinations of techniques targeting the promotion of axonal regeneration and meaningful plasticity are necessary to advance the restoration of function. In the future, refinement of animal studies may contribute to greater translational success.

Keywords: rehabilitation engineering; spinal cord injury; spinal cord injury repair; neuronal plasticity; neurorehabilitation
Abbreviation: AIS = ASIA Impairment Scale

Introduction

Traumatic spinal cord injury represents a devastating but rare condition (10–83 cases per million people worldwide; Wyndaele and Wyndaele, 2006). Individuals experience impairment in their quality of life because of deficits in sensorimotor functions, the dysfunction of the autonomic system and neuropathic pain. Nevertheless, people with incomplete para-/tetraplegia can relearn the ability to perform important daily activities, regain employment (which varies between countries: 21–67%, Lidal *et al.*, 2007) and attain a life expectancy that is close to normal. Some standardized rehabilitation procedures became established only in

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the past 20 years. Nevertheless, there is still no full consensus on the most effective approaches. In fact neurorehabilitative approaches are multifactorial, vary to some degree between rehabilitative centres and are frequently lacking evidence for their effectiveness.

Today, clinical neurorehabilitative approaches in individuals with incomplete spinal cord injury are largely based on observations originally made in animal studies (Barbeau and Rossignol, 1994; de Leon *et al*., 1998; Edgerton *et al*., 2004; Girgis *et al*., 2007; Courtine *et al*., 2009). These animal-based developments of neurorehabilitative approaches are an ongoing process aimed at improving rehabilitation procedures. They can generally be viewed as training of lost/impaired sensorimotor functions. It is, however, important to acknowledge that rehabilitation after spinal cord injury also involves the learning of new tasks such as transfer training, e.g. from bed to chair, or catheterization of the bladder. In this review we will focus on the rehabilitation of sensorimotor systems involved in functional movements. In parallel, axonal regeneration and plasticity inducing interventions (Raineteau and Schwab, 2001; Blight, 2002; Raisman, 2003; Courtine *et al*., 2008; Gosh *et al*., 2010) are being investigated in animal models and are entering the clinical stage.

The impairment after spinal cord injury depends on both level and completeness of injury (Fig. 1). This review focuses on basic and clinical research to re-establish sensorimotor functions. The first part concentrates on the significance of neuroplasticity in sensorimotor systems as the basis for rehabilitation of functional movements in incomplete human spinal cord injury. We will discuss the requirements and limitations as well as perspectives of facilitating rehabilitative neuroplasticity. This concerns the training of arm movements (usually reaching and grasping) as well as leg movements (stepping) and the increasing impact that technology has on such training. Most studies involving rehabilitation approaches in people with spinal cord injury meet only the criteria of evidence grade I (retrospective, non-randomized studies, or empirical recommendation; adapted from 'Oxford levels of evidence'), or rarely grade II (at least one randomized study). Frequently, they are based on experimental studies. More reliable studies with a stronger body of evidence exist regarding the effectiveness of rehabilitation on the outcome of sensorimotor deficits in the stroke population because of the higher frequency of stroke (Kwakkel *et al*., 1999). Although the usual mechanism of injury in stroke and spinal cord injury is different (ischaemia versus trauma), rehabilitative approaches might translate well as the recovery of sensorimotor functions is similar between ischaemic and traumatic spinal cord injury (Iseli *et al*., 1999). Further, in both stroke and spinal cord injury, neuroplasticity is the key to overcoming injury-induced loss of CNS tissue and the subsequent sensorimotor deficits. In this review, we discuss stroke studies concerning only the optimal duration and intensity of training, which we suggest can be translated to people with spinal cord injury. Therefore, the decision for an appropriate treatment of individuals with spinal cord injury should be based on solid experimental evidence [e.g. repeatable and strong effects in rodents, such as described by Edgerton *et al*. (2008)] to restore sensorimotor functions in a greater subject group suffering comparable impairment, such as post-stroke patients (*cf.* Kwon *et al*., 2013).

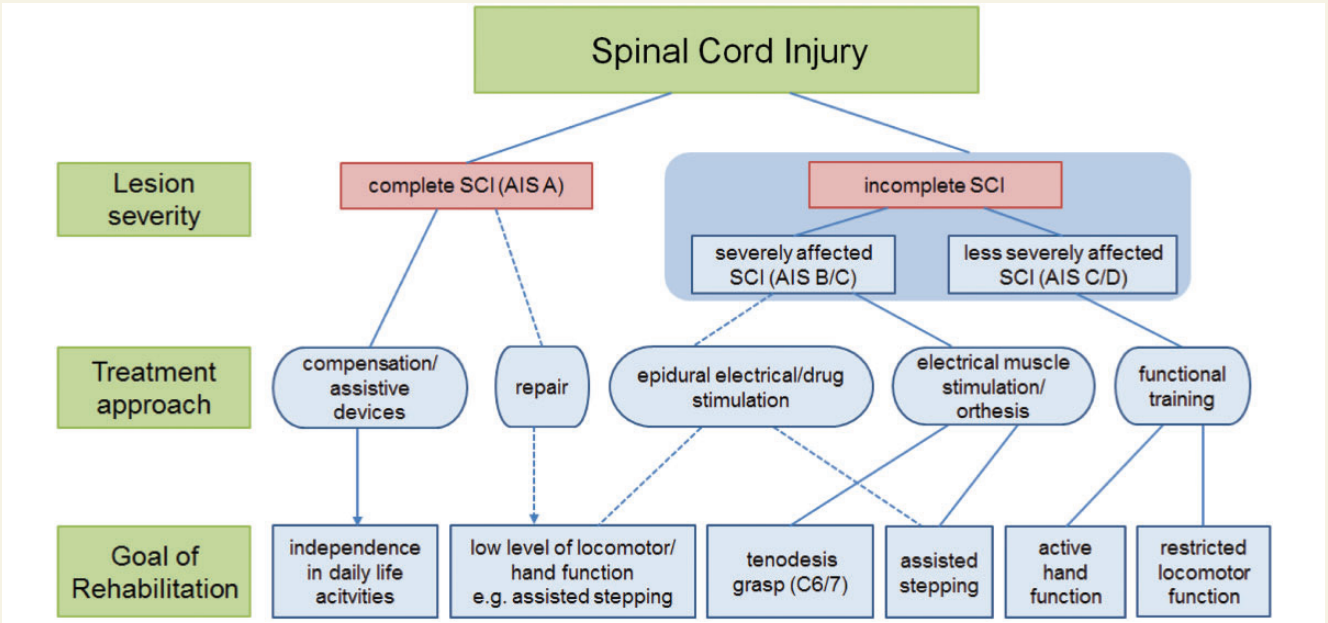

Figure 1 Rehabilitation of a spinal cord injury (SCI). Schematic overview of actual perspectives of rehabilitation approaches (circular borders) to influence the outcome of a spinal cord injury (angular borders). The individual impairment depends not only on the 'lesion severity' but also on the level of lesion. The selection of an appropriate approach has to be based on an early prediction of outcome and the completeness of injury, respectively. Solid lines indicate currently applied approaches, interrupted lines indicate interventions being on translation to human application.

The second part of the review deals with current approaches and perspectives on the restoration of function by compensating for the loss of descending input through either the stimulation of spinal networks or the restoration of descending input within the spinal cord. In combination with rehabilitative training, repairing the spinal cord will be essential for individuals with complete spinal cord injury. Although several approaches succeeded in moderately inducing regeneration and plasticity in animal models of spinal cord injury, translational studies in human subjects to date have shown no convincing effects. Possible reasons for this drawback and the hurdles of translational research will be discussed.

Clinical aspects of rehabilitation: role of neuroplasticity

Basic aspects

Neuroplasticity comprises the adaptive (including maladaptive) changes within spared neuronal circuitries and thus reflects the reorganization of the nervous system after it has been injured. Neuroplasticity after spinal cord injury occurs at several anatomical and physiological levels of the CNS, i.e. spinal cord, brainstem and cortex (Bruehlmeier *et al*., 1998; Jurkiewicz *et al*., 2007; Onifer *et al*., 2011). It includes changes in synaptic formations and synaptic strength (Rioult-Pedotti *et al*., 2007), axonal sprouting (Bareyre *et al*., 2004) and changes of intracellular properties (Boulenguez *et al*., 2010; Murray *et al*., 2010). There is also a spontaneous recovery of sensorimotor functions within the first few months after a spinal cord injury because of factors such as the resolution of neuropraxia (Curt *et al*., 2008) and remyelination of spared axons. It is hard to distinguish the relative contributions of these factors to recovery and there might be an overlap of mechanisms involved in the recovery of neuronal excitability (Murray *et al*., 2010).

In this review we use the term 'neuroplasticity' to denote adaptations in the sensorimotor systems after the acute stage of spinal cord injury, i.e. in the stable phase ~3 months after injury. Changes in sensorimotor system function can be reliably determined by assessing the neurological status (clinical and functional examinations) and electrophysiological recordings (impulse conductivity of the spinal cord and of peripheral nerves by recordings of somatosensory-evoked potentials and neurographic examinations, respectively; Curt *et al*., 2004). According to these assessments, performed over 1 year in individuals with spinal cord injury, most of the recovery of sensorimotor deficits and of somatosensory evoked potentials takes place over 12 to 15 weeks (Curt *et al*., 2008). At later stages after the acute injury, a stable phase dominates during which training-induced changes can still be initiated (Wirz *et al*., 2005; Dobkin *et al*., 2006*a*; Harkema *et al*., 2011; Field-Fote and Roach, 2011). Recovery of motor functions does not solely rely on neuroplasticity, but also on compensation and adaptation. For example, through the assistance of the non-, or less affected limbs (Curt *et al*., 2008). In the case of locomotor function, the affected leg shows little change in the leg muscle EMG pattern despite a gait recovery (den Otter *et al*., 2006). In particular at an early stage restoration of function is achieved by adaptive changes that are based on neural plasticity and, therefore, can hardly be separated. Nevertheless, compensation and adaptation can be viewed as a form of motor learning and thus, by definition, as neuroplasticity.

For individuals with spinal cord injury, functional training is the most effective approach to direct and enhance plasticity as a mean to recover motor function. Functional training can be defined as the direct/task specific training of a motor function (e.g. walking; reach and grasp movements). The mechanisms underlying the effects of facilitating neuroplasticity by functional training have been explored in rodent (de Leon *et al*., 1998; Edgerton *et al*., 2004, 2008; Girgis *et al*., 2007; Courtine *et al*., 2009) and cat models of spinal cord injury (Barbeau and Rossignol, 1994; de Leon *et al*., 1998; Barbeau and Fung, 2001; Edgerton *et al*., 2004). Using these animal models, rehabilitation of sensorimotor function after spinal cord injury is directed toward training lost/impaired movements (Edgerton *et al*., 2008). Among others, these studies demonstrate that training rats or cats with a transected spinal cord on a moving treadmill leads to a partial recovery of locomotor ability. Thus, neuronal circuits for locomotion in the spinal cord can 'learn' by training independently of the connection to the brain. The mechanisms underlying this training-induced plasticity that lead to an improved recovery of locomotion include, among others, the adaptation of neurotransmitter systems within the spinal cord (glycinergic and GABAergic systems), the upregulation of brain derived neurotrophic factor (BDNF) and enhanced collateral sprouting (reviewed in Fouad and Tetzlaff, 2012). Based on these animal studies, training of functional movements (e.g. stepping) was successfully translated to individuals with incomplete spinal cord injury (Dietz *et al*., 1995; Wernig *et al*., 1999; Dietz and Harkema, 2004; Harkema *et al*., 2012). In the future when training becomes combined with plasticity-promoting treatments, such as pharmacological and electrical stimulation-based approaches (Chen *et al*., 2006; Courtine *et al*., 2009; Cortes *et al*., 2011; Lamy, 2011), the role of neuroplasticity in enhancing recovery of function might become even more important.

Facilitation of plasticity

Comparable with what has been shown in animal studies, locomotor training following spinal cord injury can improve locomotor ability even in individuals with a low motor score (evidence grade II; Dietz and Harkema, 2004). By unloading the body and standing on a moving treadmill, individuals with spinal cord injury are enabled to perform rudimentary stepping movements. These movements evoke an appropriate afferent input to the spinal cord leading to leg muscle activation comparable with that during walking, which is the basis for the promotion of meaningful neuroplasticity (Dietz and Harkema, 2004). The benefit of such functional locomotor training does not depend on the approach used. That is, body weight supported treadmill training is equally effective as assisted over-ground walking (Dobkin *et al*., 2006*a*; Musselman *et al*., 2009; Alexeeva *et al*., 2011; Field-Fote and Roach, 2011). However, compared with earlier rehabilitation

approaches that were designed to influence physical signs, such as muscle tone, reflex activity or strengthening of muscle groups, locomotor training has been shown to be more effective in improving locomotor ability (Lucareli *et al*., 2011). Such functional training leads to a task-specific improvement of leg muscle activation and, consequently of locomotor ability with only little increase in voluntary leg muscle force (Martino, 2004; Wirz *et al*., 2006). Even in subjects with severe spinal cord injury, locomotor ability can be improved by training with assisted leg movements and body unloading. This is associated with an increase in patterned leg muscle activity that enables a reduction of body unloading during stepping (Dietz *et al*., 1995; Harkema, 2001) and a strengthening of spared descending pathways (Thomas and Gorassini, 2005). Besides facilitation of neural plasticity it is expected that also changes in muscle properties, associated with the training, contribute to the improvement of function (Howald, 1982).

Also in chronic incomplete spinal cord injury, when no more spontaneous recovery can be expected, an improvement in mobility can be achieved by functional training (Wirz *et al*., 2005; Field-Fote and Roach, 2011; Hubli *et al*., 2012; van Hedel *et al*., 2005). The gain in function achieved during such a specific training in the stable phase of a spinal cord injury might mainly be attributed to plasticity. In motor complete spinal cord injury, a locomotor EMG pattern can be both evoked and strengthened by training although leg movements have to be permanently assisted (Dietz *et al*., 1995; Harkema, 2001; Hicks *et al*., 2005).

Factors that enhance the recovery of locomotor function in stroke are, for example, longer training times (>1 h per day; Kwakkel *et al*., 1999), high intensity training (Globas *et al*., 2012), as well as asymmetric (Reisman *et al*., 2007) and faster leg movements (Pohl *et al*., 2002). Although all of these studies concern individuals with stroke, they might be translated to the rehabilitation of subjects with spinal cord injury. Furthermore, based on the knowledge that arm movements contribute to bipedal gait, locomotor ability might be improved by involvement of the upper limbs in training (Dietz, 2002; Kloter *et al*., 2011; Kloter and Dietz, 2012; de Kam *et al*., 2013).

The question regarding the early timing of a training therapy after spinal cord injury is still unresolved. Animal models indicate that there might be a 'therapeutic window' for rehabilitation after an injury (Norrie *et al*., 2005; Krajacic *et al*., 2009). In subjects with a spinal cord injury such a therapeutic window has not yet been defined although there is evidence that an early onset of training might be favourable (Dobkin *et al*., 2006; Winchester *et al*., 2009; Harkema *et al*., 2011). Of course, spinal shock associated with flaccid paresis and problems in circulation prevents a locomotor training programme in the acute/early stage after trauma. However, this might not necessarily be a disadvantage as rodent experiments indicate that training onset that is too early might be deleterious to motor recovery (Maier *et al*., 2009).

For the selection of people with spinal cord injury who might profit most from a locomotor training programme, an early prediction of ambulatory function is helpful. For example, rehabilitation of people with an (almost) complete spinal cord injury and an unfavourable prediction, rehabilitation should be focused on wheelchair driving and on other neurological deficits rather than on the lost stepping ability. Using clinical and electrophysiological assessments, a reliable prediction of stepping ability can be made that consequently allows the planning of rehabilitation procedures, e.g. locomotor training, within 4 weeks after a spinal cord injury (Curt *et al*., 2008; Zörner *et al*., 2010; van Middendorp *et al*., 2011). The essential criteria for a such a stratification are the initial lower limb motor scores combined with preservation of spinal impulse conductivity (i.e. presence of tibial somatosensory potentials; Curt *et al*., 2008; Zörner *et al*., 2010) or, combined with lower limb light touch sensation (van Middendorp *et al*., 2011).

Physiological requirements to facilitate plasticity

Training effects depend on a number of physiological prerequisites (Table 1 and Fig. 2) necessary to evoke a pattern of muscle activation similar to that found in individuals without injury of the nervous system as this is required to facilitate meaningful plasticity. A crucial factor that is needed to trigger a locomotor EMG pattern in individuals with spinal cord injury is afferent input from load receptors (Harkema *et al*., 1997; Dietz, 2012). This statement is based on the observation that without loading the sole of the foot during the stance phase no meaningful leg muscle activation occurs in individuals with complete spinal cord injury during supported stepping. Proprioceptive inputs from leg extensor muscles, and probably from mechanoreceptors in the sole of the foot, provide load-related afferent information. In addition, corresponding to studies in cats (Kriellaars *et al*., 1994; Pearson, 2008), hip extension movements, i.e. hip-joint related afferent input (but less knee or ankle joint excursions) are essential for the initiation of the swing phase and the generation of a locomotor EMG pattern in people with incomplete spinal cord injury (Dietz *et al*., 2002).

Spastic muscle tone is required to induce a locomotor EMG pattern during assisted locomotion in individuals with motor (in) complete spinal cord injury (Dietz *et al*., 1995). In addition, spastic muscle tone can compensate in part for the spinal cord injury-induced loss of supraspinal drive (Dietz and Sinkjaer, 2007). Secondary changes in mechanical muscle fibre properties after a CNS damage lead to a regulation of muscle tone during functional movements at a simpler level, i.e. without modulated muscle activation. This enables the patient, for example, to support the body during the stance phase of gait. Consequently, the application of the noradrenergic agonist clonidine (a potent antispastic drug) abolishes tonic leg muscle activity and leads to flaccid paresis of leg muscles, which prevents training effects (Dietz *et al*., 1995). Therefore, antispastic medication should be kept to a minimum in ambulatory people with spinal cord injury. In non-ambulatory individuals with spinal cord injury, however, spastic muscle tone can overshoot and lead to painful spasms.

Limitations of training-induced plasticity

In humans, the amount of sensorimotor deficits and the consequent chances for a recovery of function after spinal cord injury

Table 1 Factors influencing training effects

Factor		Function	Validity	References
1.	Training duration	Locomotion Hand function	+ + (stroke) ?	Kwakkel *et al*., 1999
2.	High intensity training	Locomotor function	+ +	Barbeau and Rossignol, 1994; Dietz and Harkema, 2004; Curt *et al*., 2008
3.	Movement velocity	Locomotion Hand/arm function	+ + (stroke) ?	Pohl *et al*., 2002
4.	(Spastic) Muscle tone	Locomotion Hand function	+ + ?	Dietz *et al*., 1995
5.	Augmented feedback	Locomotion Hand function	+ + +	Riener *et al*., 2006; Kamper 2012
6.	Virtual reality	Locomotion Hand function	+ +	Mirelman *et al*., 2009; Riener *et al*., 2010
7.	Load receptor input	Locomotion	+ +	Harkema *et al*., 1997; Dietz *et al*., 2002
8.	Hip related afferent input	Locomotion	+ +	Dietz *et al*., 2002
9.	Drug (noradrenergic; serotonergic) application	Locomotion	?	Remy-Neris *et al*., 1999; Courtine *et al*., 2009 (rodent)
10.	Epidural stimulation	Locomotion	+	Harkema *et al*., 2011

In this table the factors that might influence training effects are listed. They concern locomotor and/or hand/arm training after a spinal cord injury. The evidence differs considerably between the factors. The validity of the effects are indicated: (?) some evidence from animal experiments, no evidence in humans; (+) moderate evidence from human experiments/studies (evidence grade I); (+ +) stronger evidence from human experiments/studies for positive effects of the approach (evidence grade II).

are determined by the level and severity of spinal cord damage (Latash and Anson, 1996). In individuals with chronic incomplete spinal cord injury that are severely affected [ASIA Impairment Scale (AIS) C] some locomotor function can be re-established by intensive training (Wirz *et al*., 2005; Hubli *et al*., 2012). Nevertheless, even after such training, patients still need support (e.g. braces and/or manual assistance) to compensate for their limited stepping abilities. In contrast, individuals with less severe spinal cord injury (AIS D) usually learn to walk without support. In other words, the amount (and location) of spared spinal neural tissue determines the effectiveness of training. In the future, individuals with (almost) complete lesions might profit from a combination of training and epidural stimulation to facilitate the initiation and performance of stepping movements (Harkema *et al*., 2011).

There is also a limitation of changes in cortical structures after spinal cord injury. This is reflected in the observation that there is little remapping in the representation of limb function after spinal cord injury. In people with chronic para/low tetraplegia, somatotopical representation during movements of non/moderately affected body parts is preserved or only slightly expanded (Curt *et al*., 2002). In line with this, little cortical expansion towards more denervated lower body parts occurs when cortical areas of preserved limb function are stimulated (Freund *et al*., 2011). From a clinical point of view, these results are not surprising as upper limb function hardly profits from cortical areas denervated from lower limbs during rehabilitation.

Age also limits plasticity and the subsequent restoration of function after spinal cord injury. Although similar results were obtained regarding the recovery of neurological deficits in young and older individuals, older patients have greater problems in translating this recovery into improvements of daily life activities (Jakob *et al*., 2009). Therefore, older individuals would probably profit from age-adapted rehabilitation programmes, e.g. to focus the training on a limited number of everyday functions at home.

Also, biological rehabilitation confounders have to be considered (*cf.* Dobkin 2004). Co-morbidity, in particular infections, can have a limiting effect on the neurorehabilitative potential not only for neuroimmunological processes (Moreno *et al*., 2011) and stroke (Vermeij *et al*., 2009) but also, as shown recently, for spinal cord injury (Failli *et al*., 2012).

Another limitation of training found in animal models is the observation that specific training can interfere with untrained tasks (de Leon *et al*., 1998; Girgis *et al*., 2007). Training effects are known to be fairly task-specific (Edgerton *et al*., 2008). The finding that the training of one task limits another has, however, not yet been described in the clinical setting. Further investigations of the interaction of training paradigms appear warranted.

Lastly, following complete thoracic spinal cord injury, training focuses on motor skills relevant to the individual, including wheelchair propulsion, transfer and muscle strength. In such a condition, adaptations of the nervous system can hardly overcome the lack of descending control.

Immobility: maladaptive plasticity

There are a number of maladaptive changes after spinal cord injury such as neuropathic pain, autonomic dysreflexia and circulation failure. For the sensorimotor systems, maladaptive plasticity includes changes in neuronal function below the level of lesion (Dietz *et al*., 2009; Boulenguez *et al*., 2010; Murray *et al*., 2010).

During recent years, observations were made indicating that spinal neuronal circuitries deprived of supraspinal drive develop a neuronal dysfunction. This dysfunction is reflected by a loss of action potentials below and remote of the level of lesion (Lin *et al*., 2007), an exhaustion of leg muscle EMG activity during

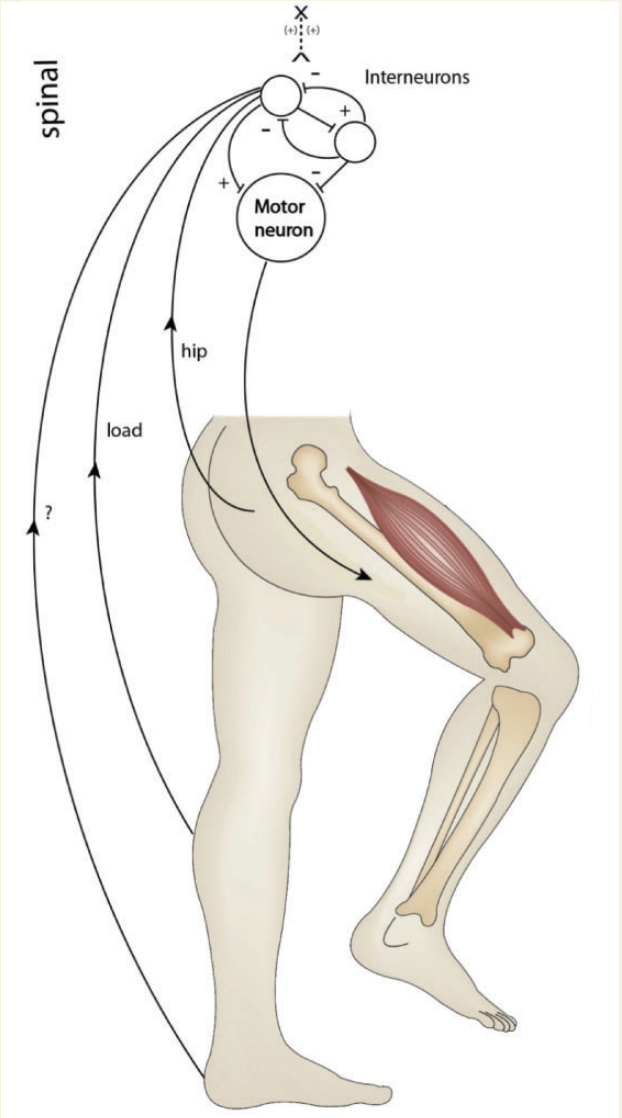

Figure 2 Neuroplasticity after spinal cord injury. Schematic drawings showing the mechanisms underlying neuroplasticity after spinal cord injury. The spinal neuronal circuits become activated by an appropriate afferent input leading to the generation of a locomotor EMG pattern and, consequently, to training effects. The equilibrium between inhibitory and excitatory signals within the neuronal circuits remains preserved. Severely affected spinal cord injury subjects become not trained for their locomotor ability. In these cases the neuronal circuits become not activated and excitatory activity weakens. This leads to a bias of inhibitory signals and, consequently, to an exhaustion of leg muscle EMG activity during assisted stepping (adapted from Dietz, 2010).

assisted locomotion (at a pre-motor neuronal level), and a change in spinal reflex behaviour (humans: Dietz and Müller, 2004; Dietz *et al*., 2009; rodents: Lavrov *et al*., 2006). The development of dysfunction seems to depend on the loss of activity in neuronal circuitries below the level of the injury in people with spinal cord injury rather than on the completeness of the injury (Dietz *et al*., 2009). Consequently, in severely affected but incomplete spinal cord injury (i.e. AIS C), the dysfunction is suggested to be influenced positively by an intensive training approach (Hubli *et al*., 2012). The occurrence of neuronal dysfunction might be because of an undirected synaptic plasticity (Beauparlant *et al*., 2013) leading to an imbalance of inhibitory and excitatory activity within neuronal circuitries with a bias towards an inhibitory drive (Dietz, 2010; *cf* Fig. 2). This assumption would be in line with the observation of an increased activity of inhibitory signals to neurons in spinalized rats (Ichiyama *et al*., 2011). Accordingly, an intensive training programme in rats re-establishes a balance between inhibitory and excitatory signals in spinal locomotor networks (Ichiyama *et al*., 2011).

The success of future repair interventions critically depends on the integrity of neuronal function below the level of lesion, e.g. non-exhausting leg muscle activation. Consequently, countermeasures have to be developed to prevent the occurrence of neuronal dysfunction in non-ambulatory individuals.

Special aspects of upper limb rehabilitation

Upper limb function is impaired in ~50% of individuals with spinal cord injury because of the cervical location of the injury. The resulting functional impairments depend on the level and completeness of damage to the cervical spinal cord. For individuals with tetraplegia even a small gain in hand function has the highest priority (Anderson, 2004). Also for the rehabilitation of impaired arm movements in people with tetraplegia, facilitation of plasticity by functional training (e.g. reach and grasp movements) prevails. Basic research has only just begun to investigate forelimb function after spinal cord injury (Girgis *et al*., 2007; Kanagal and Muir, 2008; Maier *et al*., 2008). It was reported that in rodents with cervical spinal cord injury reaching training promotes neuroplasticity and task-specific recovery (Girgis *et al*., 2007). However, less is known about the essential factors for effective training in people with cervical spinal cord injury (Oess and Curt, 2012), or whether training-induced gains-in-function persist for a significant period of time.

After cervical spinal cord injury, training approaches and their success are influenced not only by the injury of spinal tracts but also by the damage of motor neurons and roots (amounts up to 70% of paresis in C5 to C7 lesions), leading frequently to flaccid paresis and muscle atrophy (Thomas *et al*., 1997; Dietz and Curt, 2006). Flaccid paresis can impede the re-establishment of hand function as some spastic muscle tone is required to perform simple grasp movements (Dietz and Curt, 2006). In contrast, an imbalance of muscle tone within forearm muscles with a dominance of flexor tone can also hamper the recovery of hand function. This can be prevented by inducing local muscle weakness by botulinum toxin A injections allowing a certain degree of grasp movements.

In individuals with lesions around C5, training interventions are limited allowing only 'passive hand function', (i.e. supination movement at the elbow joint) with the consequence of a low degree of self-independence. In people with lesions at C6/7, the most frequently occurring condition of cervical injuries, some hand extension movement is usually preserved, allowing a 'tenodesis

grasp'. Inducing a mild contracture of finger flexor muscles can facilitate this tenodesis grasp. Such a hand function can be trained to achieve a largely independent living. So-called 'active hand function' (which is found after lesions around C8 leaving some innervation of intrinsic hand muscles) only slightly impairs hand movements required for daily life activities as it spares the ability to perform independent finger movements.

Presently, upper limb rehabilitation after cervical spinal cord injury focuses on the training of unilateral reach and grasp movements. The application of orthoses/splinting devices can be beneficial as a means to improve the performance and accuracy of functional hand/arm movements (Mirelman *et al*., 2009; Oess and Curt, 2012). Studies on the improvement of arm/hand movements using such functional training only exist for individuals with stroke (evidence grade II; Krebs *et al*., 2008; Wolf *et al*., 2008; Langhorne *et al*., 2009; Kamper, 2012).

Compared with thoracic spinal cord injury, an injury of the cervical cord leads to a mixture of damage to central and peripheral nervous system structures. Further, the level of lesion determines the individual complex pattern of sensorimotor deficits. This requires adapting rehabilitation programmes to individuals. The complexity and variability of cervical lesions complicates the introduction of promising repair interventions.

Technology support for functional training

As soon as the concept of plasticity-based functional training became established in the early 90s, the idea of the technical assistance of impaired limb movements was considered (Dietz, 2010; Riener *et al*., 2010; Benito-Penalva *et al*., 2012). These considerations were fuelled by the notion that longer and more intensive training with a high number of movement repetitions can best be achieved using robotic training devices and that this technology also allows for a monitoring of changes in movement performance over the course of rehabilitation (Riener *et al*., 2006, 2010; Dietz, 2008; Benito-Penalva *et al*., 2012). Robotic devices can promote recovery by facilitating plasticity (Everaert *et al*., 2010) and, corresponding to conventional training, they enable the performance of motor functions, which promotes activation and strengthening of neuronal pathways to a point where assistance is no longer needed.

However, increased use of technology runs the risk of becoming uncritically applied. Considering that neuronal activity is a key for meaningful plasticity to occur (Hubel and Wiesel, 1965; Guic *et al*., 2008), a robotic device should not overtake function. This requires an active involvement of the patient in movement performance. Just moving limbs does not lead to a meaningful muscle activity and, consequently, no training effect can be expected. Therefore, the robotic support provided has to be kept to a minimum so as to challenge the patient's own effort for movement performance (Reinkensmeyer *et al*., 2004; Field-Fote and Roach, 2011). Consequently, robotic-assisted training should be tailored to the individual patient's needs in order to challenge his/her own contribution to movement performance and some patient groups might specifically benefit from such training (Benito-Penalva *et al*., 2012).

Another advantage of robotic devices is that they facilitate training for people with severe spinal cord injury (e.g. AIS C, sensorimotor incomplete/non-functional) at a stage where other forms of training (e.g. over-ground stepping with support) are costly and require more resources, i.e. assistance/support by at least two individuals. In addition, robotic devices have been designed to facilitate and standardize unilateral arm/hand training with the inclusion of both virtual reality (Takahashi *et al*., 2008; Kamper *et al*., 2012) and haptic (Riener *et al*., 2006; Mirelman *et al*., 2009) experiences. This not only makes training more engaging for the patient, but can also provide augmented feedback about movement performance.

In conclusion, the technology of robotic devices in the rehabilitation of sensorimotor deficits is still in an early stage (Krebs *et al*., 1998; Dietz, 2012). It also has to be kept in mind that such technologies are not superior to other approaches of functional training *per se* (Dobkin *et al*., 2006; Duncan *et al*., 2011; Dobkin and Duncan, 2012). However, they allow longer training times in patients with severely impaired sensorimotor function. The development of future robotic devices and their effective use is a challenge that can only be overcome by the close cooperation between engineers and medically trained rehabilitation specialists, as well as multicentre studies to confirm efficacy of these rehabilitative strategies.

Preclinical approaches to restore function

Plasticity promoting approaches such as functional training to improve outcome are restricted to people with incomplete spinal cord injury. The perspectives for regaining lost function in completely paralysed individuals (~60%) will be presented in the second part of this review. Approaches will be discussed that are directed at the restoration of function in individuals with severe incomplete or complete spinal cord injury (i.e. AIS A/B). An overview of current approaches and their intentions are summarized in Fig. 1.

Activating spinal neural networks

A complete thoracic spinal cord injury deprives spinal neuronal networks of the descending drive that is necessary to trigger their activation (e.g. locomotor function). Studies in animal models have demonstrated that after complete transection of the spinal cord these networks can be activated pharmacologically, by electrical stimulation, or by natural sensory afferent input (e.g. standing on a moving treadmill). Therefore, both pharmacological and epidural electrical stimulation of the thoraco-lumbar spinal cord lend themselves as potent tools to compensate for the loss of excitatory drive from supraspinal centres. Attempts to stimulate spinal networks in animal models include epidural (Iwahara *et al*., 1991; Gerasimenko *et al*., 2003; Ichiyama *et al*., 2005) and intraspinal stimulation (Barthélemy *et al*., 2007; Mushahwar

et al., 2007). Both approaches have supported the idea that stimulation can be used to initiate locomotor activity after complete spinal cord injury or to assist with the execution of locomotor movements in incomplete lesions. Compared with direct muscle stimulation (functional electrical stimulation), which has frequently been applied to enable motor function (Thrasher and Popovic, 2008; Everaert *et al*., 2010; Alon *et al*., 2007), stimulation of spinal networks allows for a more natural, coordinated recruitment of synergistic muscle groups and causes less muscle fatigue. A challenge of the translation of these techniques to the clinical application is the invasiveness of surgically implanted electrodes overlaying (epidural) or even penetrating (intraspinal) 'healthy' parts of the spinal cord. Epidural stimulation has moved to application in human spinal cord injury (Minassian *et al*., 2004; Harkema *et al*., 2011). A patient with motor complete spinal cord injury was able to perform voluntarily controlled (but not stepping) movements with epidural stimulation (Harkema *et al*., 2011). Thus, epidural stimulation does not only facilitate the performance of leg movements by spared descending connections but also helps to overcome a critical threshold for activating spinal neural networks and promote meaningful plasticity. This is an important observation as for the first time voluntarily controlled leg movements could be induced in a motor complete subject with spinal cord injury. Therefore, such an intervention might be a viable approach for restoration of some function in a selected group of subjects with severe spinal cord injury. It remains to be shown whether epidural stimulation will generate sufficient muscle activity in individuals with spinal cord injury to support the body during stepping and what the long-term effects of such a treatment will be.

Locomotor activity can also be facilitated pharmacologically using neuromodulators. Studies in various animal models have demonstrated that intravenous, intrathecal or the indirect application (using cells grafts) of neuromodulators, including dopamine (L-DOPA, noradrenaline or serotonin; Jankowska *et al*., 1967; Barbeau and Rossignol, 1991; Cazalets *et al*., 1992; Ribotta *et al*., 2000; Schmidt and Jordan, 2000) can trigger and facilitate locomotor rhythms. Such treatments in combination with epidural stimulation results in some recovery of locomotor function in rodents (Courtine *et al*., 2009; van den Brand *et al*., 2012).

For a translation to the application in humans some challenges have to be considered. The effects of neuromodulating substances vary between vertebrates. Serotonin can initiate locomotor movements in the rabbit (Viala and Buser, 1969), neonatal rats (Cazalets *et al*., 1992; Kiehn and Kjaerullf, 1996), and facilitates walking in spinalized rats (Feraboli-Lohnherr *et al*., 1997) but does not initiate locomotion in the cat (Barbeau and Rossignol, 1991). In individuals with incomplete spinal cord injury, oral application of L-DOPA has no influence on the recovery of locomotion during rehabilitative training (Rémy-Neris *et al*., 1999; Maric *et al*., 2008).

Another challenge is the temporal control of pharmacological stimulation, e.g. locomotion has to be initiated and terminated at defined time points. Furthermore, the relation of electrical and pharmacological stimulation of spinal networks and the emergence of unwanted muscle activation has to be carefully considered. There is a thin line between that which constitutes a benefit versus that which constitutes a detriment and could be easily crossed by either mode of stimulation.

Presently, epidural and pharmacological stimulation of the isolated spinal cord is still in an experimental stage. The current approaches of stimulation techniques are unlikely to be beneficial to a majority of patients with spinal cord injury (Domingo *et al*., 2011). With increasing severity (especially complete lesions), where both excitatory and inhibitory control of spinal networks is lacking, artificially induced motor function is difficult to use by an individual. Furthermore, the aforementioned stimulation technique is restricted to lower limb function where restricted mobility can be provided by the use of a wheelchair. Nevertheless, enhancing locomotor function with electrical stimulation remains a promising research direction.

Neural repair

Promises

A partial repair of the damaged spinal cord could avoid the problems of stimulation techniques following complete spinal cord injury. During the past decades, a number of approaches to induce regeneration in the spinal cord were moderately successful in rodent models.

The best cell candidate for a transplantation-based treatment of spinal cord injury remains a matter of investigation (Tetzlaff *et al*., 2011). Schwann cells have been studied for many years and have been demonstrated to reliably form tissue bridges following complete lesions of the spinal cord (Bunge and Pearse, 2003). Other types of grafts are auto-transplantation of olfactory ensheathing or stem cells (Fortun *et al*., 2009). Also these cells are known to be permissive for the outgrowth of lesioned axons. In the case of olfactory ensheathing cells, neither negative nor beneficial effects were found in individuals with motor complete spinal cord injury (Mackay-Sim *et al*., 2008). Also results from a larger group of individuals examined in China did not show signs of motor recovery (*cf.* Dobkin *et al*., 2006*b*). Lastly these trials were not able to detect smaller but relevant negative or positive effects because of the small number of subjects included (Mackay-Sim *et al*., 2008) or because of methodological limitations (China trial, *cf.* Dobkin *et al*., 2006).

Cell grafts on their own (not even stem cells), will likely not be sufficient to promote substantial repair of the human spinal cord because axonal regeneration beyond a graft is rarely observed in animal models. However, cell grafts can be an essential factor for combinations with other regeneration promoting treatments (Fouad *et al*., 2005; Pearse *et al*., 2007; Lu and Tuszynski, 2008). More recently alternative sources from skin-derived precursor cells show promise as they effectively promote regeneration and remyelination of axons without co-treatments in rodents (Biernaskie *et al*., 2007). Also, other cell grafts such as oligodendrocyte precursor cells might have potential in remyelinating spared axons thereby contributing to recovery (Karimi-Abdolrazaee *et al*., 2006).

The excitement about the use of stem cells has taken a major hit by the interruption of the GERON trial and the fact that the tumour risk of such a treatment cannot be ignored. Nevertheless,

an encouraging result of a study grafting embryonic tissue comes from the Tuszynski laboratory (Lu *et al*., 2012). This approach shows a significant outgrow of axons from embryonic-derived neurons over longer distances in the adult rodent spinal cord. The key to the success of this study might have been the use of the embryonic stem cells in combination with a medium involving growth factors leading to a longer survival of the cells.

Pharmacologically, a promising candidate for promoting repair (regeneration and plasticity) is chondroitinase ABC, a chondroitin sulphate proteoglycan digesting enzyme (Fawcett, 2009). This enzyme has repeatedly demonstrated its ability to allow axonal regeneration and plasticity in different animal models, currently making it one of the most appreciated experimental treatments. Similarly, the application of NogoA (a prominent myelin associated inhibitor) neutralizing antibodies has resulted in significant neurite growth-promoting effects in rodent and primate spinal cord injury models (Zörner and Schwab, 2010). Recently, a phase I trial has been successfully completed.

Many experimental treatments address the inhibitory environment of the adult CNS and result in only moderate axonal regeneration. An alternative approach focuses on a cell intrinsic factor/pathway determining regenerative abilities of neurons, i.e. PTEN/mTOR (phosphatase, phosphatase and tensin homolog/mammalian target of rapamycin). The results of manipulating this pathway using genetically modified mice indicate that regeneration of corticospinal tract fibres following incomplete spinal lesions is possible (Liu *et al*., 2010).

For the success of all regeneration- (and plasticity) inducing therapies it will be of crucial importance that axons form correct connections. This fine-tuning of new connections might be facilitated by functional training as demonstrated in animal models (García-Alías *et al*., 2009). However, to demonstrate that new connections are functionally meaningful is challenging. An example where adaptive changes/rewiring resulted in new indirect connections (with different transmission speed) of cortical signals through the red nucleus has been shown by the Schwab group (Raineteau *et al*., 2001). In this study the rewiring was paralleled by significant recovery. Furthermore, it has been demonstrated that adaptations in descending tracts (especially collateral sprouting) are contributing to spontaneous and training-induced recovery (Weidner *et al*., 2001; Bareyre *et al*., 2004; Courtine *et al*., 2008; Krajacic *et al*., 2010) indicating that in the case of incomplete spinal cord injury, new/alternative connections offer a promising substrate for rehabilitative training.

Challenges

Over 30 years of research to repair the injured spinal cord did not result in the successful translation of treatments that promote functional recovery from animal models to the clinical setting. This lack of clinical success stands in contrast with many promising results in animal models that have been reported. This discrepancy is raising doubts about the quality of reports from animal models that are frequently flawed, for example, by a reporting bias because of missing data and a lack of negative results (Ioannidis, 2005; Hunter, 2011). It might, in part, be rooted in insufficient communication/cooperation between basic and clinical scientists, e.g. to explore animal spinal cord injury models that reflect best the human condition (Metz *et al*., 2000). But, it would be wrong to put the blame exclusively on inadequate spinal cord injury animal models.

One reason for the lack of successful translation concerns unrealistic expectations, such as anticipating a cure, although only small benefits are found in animal models. Such expectations are repeatedly fuelled by overstated headlines in the media (Bubela and Caulfield, 2004). For example, studies in animal models reported regeneration of a few axons over a few millimetres, which 'is a far cry from what might be needed in humans with cervical spinal cord injury to reconstitute a meaningful recovery of lower extremity function' (Tansey *et al*., 2012). Considering the relatively small functional benefits of treatments found in standardized and controlled animal models of spinal cord injury, it is not surprising that when these treatments are applied in the clinical setting, where a much higher variability in lesion size and location exists, no effects are found.

Frequently it is also overlooked that treatments are often tested in animal models with incomplete lesions because most neuronal growth inducing approaches rely on residual tissue bridges to achieve growth/plasticity of spared axons. Thus, in complete spinal cord transection these treatments can only promote benefits if the lesion site is bridged. In clinical trials of spinal cord injury, typically the first safety phase is performed in individuals with complete lesions where usually no sufficient tissue bridges exist (Dietz and Curt, 2006). Another factor that influences the development of effective treatments to repairing the injured spinal cord is that neurite growth is inhibited by a variety of factors, such as myelin-associated inhibitors including NogoA (Zörner and Schwab, 2010), a lack of neurotropic support, developmental changes in neurons restricting their regenerative ability (Qiu *et al*., 2002), chondroitin sulphate proteoglycans (Fawcett, 2009) in the scar tissue formed around the lesion site (Hermanns *et al*., 2001) and in the perineuronal nets (Massey *et al*., 2006). Combinatorial treatments addressing more than one of these impediments for neurite growth currently have a high priority in basic research. However, such treatments are challenging, due not only to technical difficulties, but also to unpredictable treatment interactions and the necessity of a large number of controls.

Limitations of animal models also include different projections of spinal tracts in different species determining the degree of recovery. For example, when comparing primates to rodents the corticospinal tract has a higher degree of midline crossing collaterals, enabling a higher degree of recovery in primates as compared to rodents (Rosenzweig *et al*., 2010). In addition, quadrupedal locomotion allows more post-lesion activities and thus self-training compared with bipedal walking in humans (Fouad *et al*., 2000; Caudle *et al*., 2011). Furthermore, treatments in animal models are frequently applied directly after injury, (which is clinically unrealistic), with injury types typically not found in patients (e.g. incision lesions rather than contusions over two to three segments in patients; *cf.* Metz *et al*., 2000).

Beyond these limitations, results from animal models frequently cannot be repeated in the same animal model (Steward *et al*., 2006). The field has recognized this problem and has responded by repeating studies and promoting publication of 'negative' results (see issue 233 of Experimental Neurology, 2012), as well as

by encouraging critical discussions of deficiencies in research approaches (Liu *et al*., 2010; Sena *et al*., 2010; Kwon *et al*., 2011; Steward *et al*., 2012). Such deficiencies include a low statistical power of animal experiments with relatively small numbers of animals, resulting in the probability of false positive results (Ioannidis, 2005) and a bias to publish such positive results (Sena *et al*., 2010). Another bias might occur because of an invested interest in a treatment with the consequence that scientists are reluctant to publish negative results of a therapy. This idea was fostered by the results of a survey performed recently (Kwon *et al*., 2010): 47% of the participants strongly agreed and 42% mildly agreed to this statement. But even if there was no invested interest, the survey indicates that scientists generally are 'reluctant to publish their own negative result on a therapy'.

In general, it has to be recognized that not all scientific achievements in basic research in spinal cord repair do necessarily advance the field towards clinical trials. Treatments designed to promote axonal regrowth have a substantial risk potential (e.g. enhanced pain). Therefore, progress has to be made in understanding the physiological changes in the injured spinal cord as well as the drug interactions and possible side effects of a treatment. Such contributions are important for developing safe and reliable treatments in the future. Nevertheless, although there have been disappointing reports about abandoned clinical trials over the recent years, there are new promising treatments promoting axonal regeneration and/or sprouting (Fig. 3). The clinicaltrials.gov registry gives testimony that several small open label trials are under way.

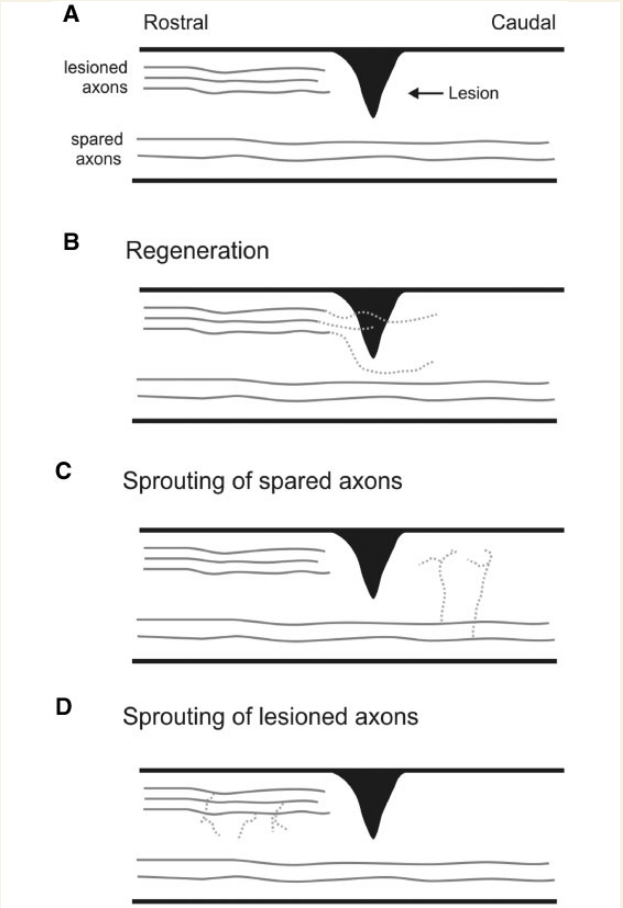

Figure 3 Axon regeneration versus sprouting after a spinal cord injury. The figure summarizes the mechanisms of regeneration and sprouting after a spinal tract damage. (**A**) An injury severs some axons while sparing others. (**B**) Regeneration is the growth from the injured axonal tips. Regenerating axons can grow through or around a lesion site. (**C**) Sprouting of spared (i.e. uninjured) axons. They often sprout into a denervated area, in response to an injury elsewhere in the CNS. (**D**) Sprouting can also occur from uninjured portions of injured neurons (i.e. growth from uninjured axonal branches or from the main axonal shaft de novo proximal to the injury site as shown here; from Zheng and Fouad, 2012).

Perspectives

During the past 20 years, basic and clinical research activities have strongly advanced the field of spinal cord research and, consequently, of rehabilitating people with spinal cord injury. Principles to promote neuroplasticity derived from basic research have become successful in terms of their translation to the human condition and will further be refined and supplemented by advanced technology. Treatments directed at improving function by pharmacological or electrical stimulation are on the verge of translation, but face substantial challenges. Such challenges are found throughout the clinical sciences (e.g. stroke; Narayan *et al*., 2002). Nevertheless, the knowledge gained by basic research, e.g. the refinement of stimulation techniques or search for appropriate animal models, will serve as a basis for successful translations. This makes the perspectives for some restoration of lost functions even after motor complete spinal cord injury promising.

Conclusions

In people with incomplete spinal cord injury neuroplasticity can be facilitated and refined by training of upper and lower limb movements with the goal to individually optimize the functional outcome. The prognosis of outcome after injury by clinical and electrophysiological examinations allows an early selection of appropriate training approaches. These should focus on relearning specific everyday movements. An effective rehabilitation of sensorimotor systems is based on physiological requirements that lead to a meaningful muscle activation. For severely affected people with spinal cord injury [AIS A/B/(C)], the prospects are less promising. Stimulation approaches might facilitate stepping but hardly upper limb movements. Repair interventions are as yet, not successful. At a cervical level, where repair would be most required to improve hand/arm function, limitations for repair exist due to a combination of damage to both spinal tracts and motor neurons/ventral roots. Thus, basic research needs to continue to develop, to repeat and to combine treatments with the aim to repair the injured spinal cord. Lastly, guidelines are needed regarding what should be translated and what can realistically be expected from reliable and safe treatments (Kwon *et al*., 2010).

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